

Screening for Middle East respiratory syndrome coronavirus infection in hospital patients and their healthcare worker and family contacts: a prospective descriptive study

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Abstract

The Saudi Arabian Ministry of Health implemented a pro-active surveillance programme for Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV). We report MERS-CoV data from 5065 Kingdom of Saudi Arabia individuals who were screened for MERS-CoV over a 12-month period. From 1 October 2012 to 30 September 2013, demographic and clinical data were prospectively collected from all laboratory forms received at the Saudi Arabian Virology reference laboratory. Data were analysed by referral type, age, gender, and MERS-CoV real-time PCR test results. Five thousand and 65 individuals were screened for MERS-CoV: hospitalized patients with suspected MERS-CoV infection ($n = 2908$, 57.4%), healthcare worker (HCW) contacts ($n = 1695$; 33.5%), and family contacts of laboratory-confirmed MERS cases ($n = 462$; 9.1%). Eleven per cent of persons tested were children (<17 years of age). There were 108 cases (99 adults and nine children) of MERS-CoV infection detected during the 12-month period (108/5065, 2% case detection rate). Of 108 cases, 45 were females (six children and 39 adults) and 63 were males (three children and 60 adults). Of the 99 adults with MERS-CoV infection, 70 were hospitalized patients, 19 were HCW contacts, and ten were family contacts. There were no significant increases in MERS-CoV detection rates over the 12-month period: 2.6% (19/731) in July 2013, 1.7% (19/1100) in August 2013, and 1.69% (21/1238) in September 2013. Male patients had a significantly higher MERS-CoV infection rate (63/2318, 2.7%) than females (45/2747, 1.6%) ($p = 0.013$). MERS-CoV rates remain at low levels, with no significant increase over time. Pro-active surveillance for MERS-CoV in newly diagnosed patients and their contacts will continue.

Keywords: Clinical, coronavirus, demographic, diagnosis, MERS-CoV, Middle East, real-time PCR, sample type, SARS, screening, viral load

Original Submission: 29 December 2013; **Accepted:** 17 January 2014

Editor: M. Drancourt

Article published online: 24 January 2014

Clin Microbiol Infect 2014; **20**: 469–474

10.1111/1469-0691.12562

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Introduction

Understanding the natural history, epidemiology and clinical presentation of new killer infectious diseases is dependent on, and influenced by, the WHO recommended surveillance strategies for case detection, which largely focus on severe

illness and microbiological testing, coupled with details from case studies. Contact-tracing activities allow for the detection of confirmed cases with a broader spectrum of illness. For infectious diseases caused by viruses, confirmed cases include only those with a positive PCR test result for viral genetic material, in accordance with the laboratory guidelines. Since the first case report of the novel Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV) in September 2012 [1], the Kingdom of Saudi Arabia (KSA) Ministry of Health (KSA-MoH) has been working closely with international collaborators and the WHO to better understand and define the epidemiological, demographic, clinical and laboratory features of the new disease. A molecular real-time PCR diagnostic test was rapidly developed after the first case, and was subsequently the method recommended by the WHO for detecting the presence of the MERS-CoV infection [2,3]. This test was used in a retrospective analysis on biobanked samples to confirm two cases of MERS from an earlier outbreak of respiratory infection in Jordan in April, 2012 [4].

Important steps for the surveillance and control of MERS-CoV infection are the early detection and isolation of patients with active MERS-CoV disease, and screening of their contacts. Surveillance studies also help in defining and monitoring transmission rates, case load, and epidemic risk assessment, and assist in instituting infection control measures with new diagnostic methods and treatments. Although MERS-CoV case detection is critically dependent on the degree of awareness of the attending physician, accurate laboratory testing is also essential in making a diagnosis. Soon after the detection of the first case of MERS in Jeddah in September 2012 [1], the KSA-MoH put in place a proactive surveillance and screening programme for inpatients admitted with respiratory illness suspected of being caused by MERS-CoV. It also included active screening of contacts of confirmed MERS cases. KSA-MoH recommendations for MERS-CoV screening are based on the WHO guidelines on case definition, detection, and contact investigations [5–7]. This led to an increase in the numbers of requests for MERS-CoV screening from hospitals throughout the KSA. We report these laboratory data on the use of real-time PCR tests on clinical samples received from 5065 individuals screened for MERS-CoV during a 12-month period, commencing from the first case detection in September 2012.

Methods

Selection of individuals for MERS-CoV screening

The KSA-MoH has implemented a pro-active early case detection and surveillance system for MERS-CoV. It recommends sending respiratory tract samples from critically ill

patients admitted to hospitals with fever and lower respiratory tract infection symptoms. Screening for MERS-CoV is also recommended for family and healthcare worker (HCW) contacts of proven cases of MERS-CoV infection. All samples are transported to and are processed by the KSA-MoH virology laboratory in Jeddah, which is accredited and regulated by the Central Board for Accreditation of Health Care Institute. Quality assurance and control for all diagnostic tests is monitored through Internal Policy Procedures and by external quality assurance schemes.

Collection of clinical specimens

Respiratory specimens collected from patients and contacts were: sputum samples; nose and throat (N + T) swabs; nasopharyngeal (NP) swabs; and tracheal aspirate samples. Sputum was collected directly into a sterile, leak-proof, screw-capped sputum collection sterile container; NP swabs and N + T swabs were collected with sterile synthetic tip Dacron flocked swabs. For NP specimens, the swabs were inserted through the nostril, parallel to the palate, into the nasopharynx. Swabs were left in place for a few seconds to absorb secretions. For N + T swabs, both nostrils and the throat were swabbed with separate swabs. All swabs were placed immediately into sterile tubes containing 2–3 mL of viral transport medium. For inpatients, lower respiratory tract samples—2–3 mL of bronchoalveolar lavage fluid and tracheal aspirate—were obtained and placed into sterile, leak-proof, screw-capped sterile dry containers.

Labelling, storage and transportation of specimens

When there were short periods of transportation (≤ 48 h) of specimens to the laboratory, specimens were held in a refrigerator at 2–8°C rather than frozen; for periods exceeding 48 h, specimens were shipped on dry ice at –70°C as soon as possible after collection. Each specimen container was labelled with the patient's ID number, the specimen type, and the date on which the sample was collected. All specimens were pre-packed to prevent breakage and spillage. Specimen containers were sealed with parafilm and placed in zip-lock bags. Absorbent material to absorb the entire contents of the secondary container (containing the primary container) was placed to separate the primary containers (containing specimen) to prevent breakage.

RNA extraction

Extraction of RNA was performed with Roche MagNa Pure LC (RNA Viral isolation Kit). Sputum samples were pretreated with 2 × lysis buffer for 30 min in a shaking incubator. Swabs were placed in lysis buffer. Two hundred microlitres of each sample was added to the MagNA Pure LC plate, which contains 96 wells. Reaction reagents were then loaded and checked,

before the samples were run according to the manufacturer's instructions for nucleic acid extraction in the specimen area.

MERS-CoV screening test

A biosafety level 2 facility equipped with microbiological safety cabinets was used for the handling of clinical specimens and for extracting RNA for PCR. PCR is the recommended method for detecting the virus. At least three sites in the genome of MERS-CoV have been identified as suitable targets for the diagnostic test—the upstream E protein gene (*upE*), open reading frame (ORF) IA, and ORF IB—and sequences of the specific primers have been published. Positive controls for the *upE* screening and the ORF IA confirmation assays are available. Clinical samples were screened by real-time PCR, as previously described [6], with amplification targeting both *upE* and ORF IA for confirmation—these are standard assay used in the KSA for MERS-CoV testing. The test result was considered to be positive if both assays gave positive results. In cases of discordance between the first and second assays, or if the result was considered to be a doubtful positive result, another clinical sample was requested and analysed.

Data collection

Data from laboratory forms accompanying clinical samples received at the KSA-MoH virology laboratory specifically requesting MERS-CoV testing during the period 1 October 2012 to 30 September 2013 were collected and analysed. Demographic and laboratory PCR test data and MERS-CoV viral load data were recorded. Where data were missing from the records or where clarification was required, data were obtained through direct communication with attending physicians and other healthcare providers.

Serological testing

No serological testing data were available, because there are no validated accurate serological diagnostic tests for MERS-CoV available to date.

Statistical analyses

Demographic, clinical and laboratory descriptive data were tabulated. Univariate analysis was performed with binary logistic regression analysis. A *p*-value of <0.05 was considered to indicate statistical significance.

Results

A total of 5065 individuals (625 children and 4440 adults) were screened for MERS-CoV during the 12-month period: hospitalized patients with suspected MERS-CoV infection

(*n* = 2908, 57.4%), HCW contacts (*n* = 1695; 33.5%), and family contacts of laboratory-confirmed MERS cases (*n* = 462; 9.1%) (Fig. 1). There were 108 cases (99 adults and nine children) of MERS-CoV infection detected during the 12-month period (108/5065, 2% case detection rate) (Table 1). Of 108 MERS cases, 45 were females (six children and 39 adults) and 63 were males (three children and 60 adults). Of the 99 adults with MERS-CoV infection, 70 were hospitalized patients, 19 were HCW contacts, and ten were family contacts. Of the nine children with MERS-CoV infection, two were hospitalized patients and seven were family contacts. A significant increase in the number of screened and tested specimens was evident over the study period (Fig. 2a), but there were no significant increases in MERS-CoV detection rates over the 12-month period (Fig. 2b). The monthly case detection rates of MERS-CoV were 2.6% (19/731) in July 2013, 1.7% (19/1100) in August 2013, and 1.69% (21/1238) in September 2013 (Fig. 2b). Male patients had a significantly higher MERS-CoV infection rate (63/2318, 2.7%) than females (45/2747, 1.6%) (*p* 0.013) (Table 2).

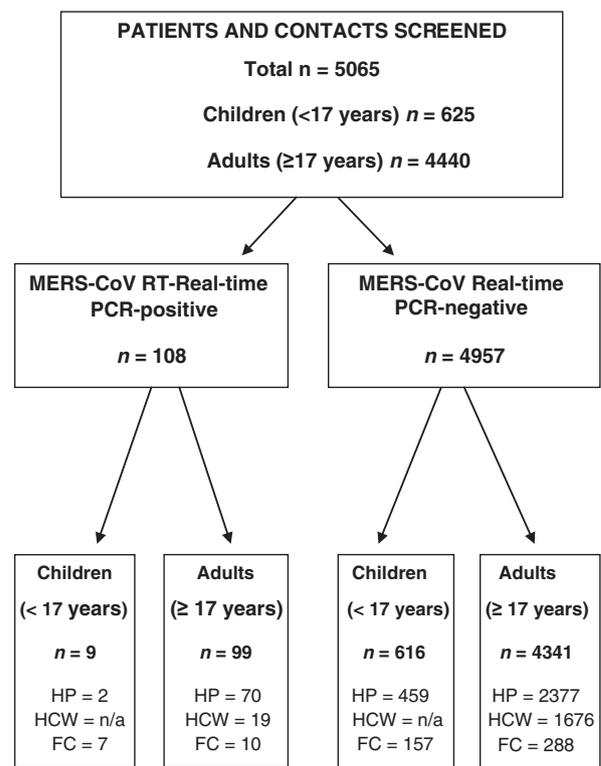


FIG. 1. Flow chart: screening of hospitalized patients and contacts. FC, family contacts; HCW, healthcare workers and their contacts; HP, hospital patients; NA, not applicable.

TABLE 1. Middle East respiratory syndrome coronavirus (MERS-CoV) screening by referral type and age group

Patients and contacts MERS-CoV real-time PCR	Children (aged <17 years)			Adults (aged ≥17 years)			All Positive ^a	Total	% Positive ^a
	Positive	Total	% Positive ^a	Positive	Total	% Positive ^a			
Hospital patients	2	461	0.43	70	2441	2.86	72	2908	2.51
HCW contacts	NA	NA	NA	19	1695	1.12	19	1695	1.12
Family contacts	7	164	4.2	10	298	3.36	17	462	3.6
Total	9	625	1.4	99	4440	2.19	108	5065	2.1

HCW, healthcare worker; NA, not applicable.
 For children: p-value for positive PCR in hospitalized patients vs. family contacts, 0.0021.
 For adults: p-value for positive PCR in hospitalized patients vs. HCWs, 0.0029; p-value for hospitalized patients vs. family contacts, 0.46; p-value for HCWs vs. family contacts, 0.025.
^aPercentage within each age group.

Discussion

Since the first KSA case report in September 2012, the KSA-MoH has recommended mandatory testing for MERS-CoV of all cases of respiratory illness requiring intensive-care admission. This is the largest study describing the incidence rates of MERS-CoV in the KSA over a period of 12 months. The real-time PCR MERS-CoV diagnostic test has been in use for detecting new MERS cases in hospitalized patients, and for screening of HCW and family contacts of confirmed MERS cases [7–11]. Six months after MERS-CoV was discovered, at the end of March 2013, there were only 17 MERS-CoV cases reported globally, nine of which were from the KSA [12]. In

light of the infrequent, but continuing, detection of sporadic MERS-CoV cases in the community and the hospital outbreak at Al-Hasa [10], the WHO constituted an Emergency Committee under the International Health Regulations to advise the Director-General on the status of the MERS-CoV situation [13]. The important issue at that time was whether MERS-CoV was going to progress to cause a major pandemic, as did the SARS epidemic in the early 2000s, which was also caused by a novel coronavirus, SARS-CoV [14].

Our results show that pro-active surveillance during the months after the Al-Hasa outbreak, which occurred in April–May 2013, showed no significant increase in the MERS case detection rates in the ensuing 8 months. The monthly positive rates of MERS-CoV were 2.7% in July 2013 and then 1.7% in August and September 2013. The initial increase in July 2013 was related to the intensification of the surveillance of MERS-CoV in the KSA following the healthcare-related outbreak at Al-Hasa [10]. From our data, three areas of transmission can be focused on for active surveillance and screening.

The first pattern is the occurrence of sporadic cases in communities. The true incidence of the disease in the community is not known, and remains to be defined through case–control serological surveys when accurate, rapid, sensitive and specific serological tests become available. In the community, the asymptomatic cases or those with minimal symptoms are difficult to identify, and are usually missed. Those who become acutely ill in the community present to emergency rooms, where real-time PCR testing of respiratory samples is performed.

The second pattern of transmission is transmission within families [8]. The rate of intrafamilial transmission is not known. Our results provide an estimate of a rate of 3.6% for acquisition of MERS-CoV from close family contacts. However, this finding is not conclusive, as no serological assays were utilized for screening mild or subclinical cases. However, the finding is in agreement with previous observations of low secondary attack rates among family members or contacts of patients in the KSA and European countries [8, 15–22].

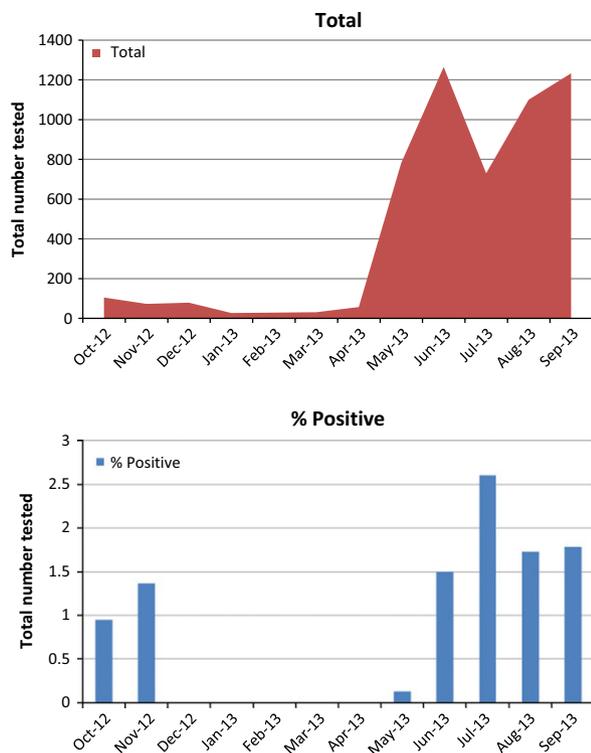


FIG. 2. Kingdom of Saudi Arabia Middle East respiratory syndrome coronavirus case screening (a) and detection rates (b) over time.

TABLE 2. Distribution of all individuals screened by age, gender and Middle East respiratory syndrome coronavirus (MERS-CoV) status

	Children			Adults		
	Number positive	Total screened	% Positive	Number positive	Total screened	% Positive
Female						
Family contacts	5	87	5.7	3	147	2.04
HCW contacts	0	0	–	15	1155	1.30
Patients	1	207	0.48	21	1151	1.82
Total	6	294	2	39	2453	1.59 ^a
Males						
Family contacts	2	77	2.5	7	151	4.64
HCW contacts	0	0	–	4	540	0.74
Patients	1	254	0.39	49	1296	3.78
Total	3	331	0.9	60	1987	3.02 ^a

HCW, healthcare worker.

^aMale patients had a significantly higher positive rate for MERS-CoV than female patients (p 0.013).

The third transmission pattern is nosocomial transmission to HCWs. In one study, seven HCWs with MERS-CoV infection were reported. Two of them were asymptomatic, and five had mild upper respiratory tract symptoms [11]. The current study sheds more light on the transmission of MERS-CoV in healthcare setting. The positivity rate of MERS-CoV by PCR was only 1.12% of all tested HCWs. Transmission within healthcare settings was retrospectively reported from Jordan [4], and then subsequently reported in France, the KSA, the UK, the United Arab Emirates, and Qatar, and included HCWs treating MERS-CoV patients [23–27]. These data suggest that the current risk of transmission within healthcare facilities remains small, and that the recommended infection control measures are adequate [6,9,13,20].

Studies of family and hospital case clusters of MERS-CoV infections in the KSA and other European countries that have reported MERS cases indicate that a spectrum of clinical illness occurs [7–9,15,16]. Reports from Tunisia and the UAE of MERS-CoV infections occurring in siblings whose father's illness was a probable MERS-CoV infection case, and the case from the UK [8,24,25], show that the siblings who are not immunocompromised only manifest mild respiratory illnesses, and do not require hospitalization. In the UK family cluster, among 33 close contacts (20 household and 13 non-household), there were only two cases (6% attack rate) of confirmed MERS-CoV infection, one with mild illness and one with severe illness [15]. There were no cases of MERS-CoV infection among 59 HCWs who were in contact with the index case without wearing full personal protective equipment [15].

The fact that we have subsequently identified milder or asymptomatic cases of MERS in HCWs, children and family members of contacts of MERS cases indicates that the severe cases represent only the tip of the iceberg, and there is a spectrum of milder clinical disease that requires definition. Our data indicate that MERS-CoV affects both genders, and,

although a few cases of MERS-CoV in children have been detected, it remains mainly a disease of adults across all age groups. To date, there is still no evidence of sustained community transmission. Despite extensive investigation and testing of thousands of contacts by the KSA-MoH, only a few instances of transmission to HCWs or family contacts have been identified. Almost all patients who died or who had been hospitalized had severe disease or other comorbidities [9,10]. The mortality rate and severity of disease are exaggerated to some degree by the detection of such cases. The case-fatality rate has fallen in recent months, owing to the detection of milder and asymptomatic cases [23–27]. The most critical characteristic of pandemic MERS-CoV strains would be progression to efficient human-to-human transmission. The number of sporadic MERS cases being reported has been small, and indicates that the virus appears to be not readily capable of rapid human-to-human transmission. Two million pilgrims from over 180 countries, and 1 million local KSA pilgrims, have very recently visited Makkah and Madinah, KSA to perform the 2013 annual Hajj pilgrimage, and have returned home after stays of between 2 and 8 weeks [28]. Millions of others will visit the KSA throughout the year for the mini-pilgrimage UMRAH, and although MERS-CoV infection rates in the KSA remain at steady, low levels, and no significant increase in the incidence of MERS-CoV infection over time is occurring, pro-active surveillance for MERS-CoV in newly diagnosed patients and their contacts will continue. The availability of more rapid and accurate serological tests will help to better define the community prevalence of MERS-CoV.

Transparency Declaration

All authors have no conflict of interest to declare.

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